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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/519,998	03/06/2000	D. Scott Wilbur	33700W003	8767

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EXAMINER	
WELLS, LAUREN Q	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/519,998	WILBUR ET AL.	
	Examiner	Art Unit	
	Lauren Q Wells	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/25/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,11-22 and 24-39* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-9,11-22,24,25 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 6-9, 11-22, 24-39 are pending. Claims 26-30 are withdrawn from consideration, as they are directed to non-elected subject matter. The Amendment filed 2/25/04, cancelled claims, 4-5, and amended claims 1, 7, 11, and 33.

Applicant's argument over the 35 USC 102 and 103 rejections are persuasive to overcome these rejection in the previous Office Action, as WO 97/29114 does not teach an alpha carboxylate or an N-methyl group in linker 1.

Applicant's arguments with respect to claims 1-3, 6-9, 11-22, 24-25, 31-39 have been considered but are moot in view of the new ground(s) of rejection. However, the Examiner will answer this argument, "Compound 56 in the Wilbur reference is only mentioned as a possible reagent and is the only compound of that type presented in the entire document". This argument is not persuasive. Whether the compound was taught one time or twenty times is not relevant. Wilbur teaches Compound 56, which is a trifunctional reagent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-22, 24-25, 31-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosis of myocardial infarction and certain cancers and treatment of certain cancers, does not reasonably provide enablement for diagnosis and treatment of human and animal conditions or diseases. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides constrained peptide derivative having the formula R1-R2-R3-R4-R5-R6-R7 where R and R7 are 1-6 amino acids where at least one is tyrosine or phenylalanine, R2 and R6 is a linking amino acid residue, R3 and R5 is 0-13 amino acids, R4 is 3-26 amino acids.

(2) The state of the prior art

The peptides of the inventions are CDR-like peptides. However, the art does not teach constrained peptides that have at least a Y or F residue in the first six position and a linking amino acid for the R2 and R6 corresponding positions.

(3) The relative skill of those in the art

The relative skill of the those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of the peptide art is very high. The true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(5) The breadth of the claims

The claims are very broad. The sequence length of the claimed peptide ranges from 7 amino acid residues to 68 amino acid residues in length. For claim 1, only 2 residues of the maximum 68 residues are disclosed. The limiting claims that limit the length of the peptide claim still claim peptides only disclose up to four amino acid resides.

(6) The amount of direction or guidance presented

The specification and the Declaration, file 12-20-96, all disclose peptides that have a maximum length of 15 amino acids. Moreover, the constrained peptides disclosed in the specification and the declaration all disclose peptides that have been cyclized through the cystine

residues. Therefore the Declaration and the specification has enabled peptides that have a maximum number 15 amino acid residues , where R4 has the sequences of CD4 , MHCII, and CDR2 fragments disclosed on table 1 on page 19 and the peptides are cyclized through cystine. The specification provides no guidance, in the way written description, peptides that have the sequence of 16-68 amino acid residues in length. For example, the specification does not provide any written description the residues that could be substituted at the R3 or R5 position. may be required. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.
As stated above, the true fact of the state of the art in peptide chemistry is expressed succinctly in the Rudinger article (see the conclusions in particular). "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study."

(7) The presence or absence of working examples

As stated above, the specification and the Declaration, file 12-20-96, all disclose peptides that have a maximum length of 15 amino acids. Therefore the Declaration and the specification has enabled peptides disclosed in the Declaration and in the specification on page 19. These peptides have a maximum number 15 amino acid residues and R4 has the sequences of CD4 , MHCII, and CDR2 fragments as disclosed on table 1 on page 19.

(8) The quantity of experimentation necessary

Since the significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine the all of the peptide analogues would not affect the property of the peptide.

Regarding this rejection, Applicant argues, "The specification teaches those of ordinary skill in the art how to make and/or use the claimed invention as a reagent. Furthermore, there are

demonstrative examples to guide the skilled practitioner through the production of such reagents". This argument is not persuasive. The Examiner agrees that the specification does teach the reagent and does exemplify the reagent. However, this is not the issue. The issue is the reagent for "diagnosis and treatment of human and animal conditions or diseases". This is neither taught nor exemplified by the instant specification.

Applicant argues, "The Office has raised no substantial evidence or analysis to challenge the presumption of enablement". This argument is not persuasive. See the above rejection, which contains substantial evidence and analysis.

Applicant argues, "There is clearly sufficient disclosure in the specification as to how the invention may be practiced". This argument is not persuasive. The Examiner is not able to find such a disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 14, 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The term "derivative" in claims 14 (line 3) and 32 (line 2) is vague and indefinite, as the metes and bounds of these claims are unascertainable. What is a derivative of avidin or streptavidin or amino-carboxy or EDTA?DTPA? Is it a hydroxyl substituted compound, an alkyl substituted compound, a nitro substituted compound. . .? The specification does not define this phrase and one of ordinary skill in the art would not be apprised of its meaning.

Regarding this rejection, Applicant argues, "the term 'derivative' does not encompass an innumerable number of chemicals, but encompasses derivatives of avidin or streptavidin (which derivatives are known to those of ordinary skill) that have essentially the same binding function to the affinity ligand". This argument is not persuasive. It is respectfully pointed out that the rejection over the term "derivative" in claims 14 and 32, is in regard to the phrases "amino-carboxy derivatives" and "EDTA and DTPA derivatives".

Applicant's argument over the phrase "avidin or streptavidin derivatives" is persuasive, as this phrase is a term of art. Even the primary reference, WO 97/29114, teaches these derivatives.

The Amendment to claims 1, 11, and 33, filed 2/25/01, is sufficient to overcome the 35 USC 112 rejection over these claims in the previous Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 11-22, 25, 31-32, 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. (WO 97/29114) in view of Wilbur et al. (Bioconjugate Chem. 1997, 8, 572-584) or in view of Rosebrough (Jn. Of Pharmacology and Experimental Therapeutics, 1993).

The instant invention is directed toward a reagent comprising a trifunctional cross-linking moiety, an affinity ligand, an effector agent, a biomolecule reactive moiety, and three optional linkers.

Wilbur et al. exemplify a trifunctional biotin reagent, wherein tricarboxybenzene is the trifunctional cross-linking moiety, biotin is the affinity ligand, maleimide is the biomolecule reactive moiety, an aryl iodide bonding moiety is the effector agent, and trioxadiamine (which contains 15 atoms) is the linker, wherein the affinity ligand is connected to the linker via a biotinamide bond. The linkers are connected to the individual components by amide bonds. The linkers contain ether groups which are hydrogen bonding atoms. Biotin binds with another molecule with an affinity constant of 106M-1 or higher and specifically binds to avidin. See page 39. On page 18, Wilbur et al. teach carboxylate active esters of hydroxysuccinimidyl and phenyl as interchangeable with maleimides. On page 23, it is taught that EDTA, DTPA, DOTA and others may provide chelates for radionulcides such as Y-90. On page 6, biotin, desthiobiotin, biotin sulfone, and iminobiotin, are taught as interchangeable affinity ligands. On pages 9-10, it is taught that trifunctional cross-linkers can be utilized without linkers.
The reference lacks an alpha carboxylate or an N-methyl group in linker 1. Wilbur et al. is applied as discussed above. The reference further lacks an exemplification of excluding linkers 2 and 3, chelating groups, radionuclides, and preferred active esters.

Wilbur et al. (Bioconjugate) teach biotin reagents for antibody pretargeting, see title. It is taught that N-methyl containing moieties are added to the biotin moiety to block biotinidase activity, thereby increasing its stability against degradation, see abstract.

Rosebrough teaches the plasma stability and pharmacokinetics of radiolabeled deferoxamine-biotin derivatives, see title. IT is taught that the introduction of an alpha-carboxylase group in the linker blocks biotinidase activity, thereby increasing the stability of biotin, see abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an N-methyl group, as taught by Wilbur et al. (Bioconjugate), or an alpha-carboxylate group, as taught by Rosebrough, into the linker between biotin and tricarboxybeneze, of Wilbur et al., because of the expectation of achieving a reagent that blocks biotinidase activity, thereby increasing the stability of the reagent, as taught by Wilbur et al. (Bioconjugate) and Rosebrough.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute an ester of hydroxysuccinimidyl for the maleimide in structure 56 of Wilbur et al. because Wilbur et al. teach these biomolecule reactive moieties as interchangeable preferable compounds for conjugation to an activated biotinylation reagent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the chelated radionuclides taught by Wilbur et al. on page 23 of the specification for the amino carboxy containing radionuclide because of the expectation of achieving similar radiotherapeutic effects and because of the expectation of achieving a radionuclide that is stabilized.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute biotin sulfone for biotin in structure 56 of Wilbur et al. because Wilbur et al. teach these biotins as interchangeable affinity ligands.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to teach structure 56 without linkers 2 and/or 3 because Wilbur et al. teach that linkers are not necessary and because of the expectation of achieving a compound that is stabilized from its medium, as it is not as reactive with it.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute homobiotin or norbiotin for the biotin taught by Wilbur et al. because adjacent homologs are considered to be obvious absent unexpected results. In re Henze, 85 USPQ 261, 263 (CCPA 1950).

It is respectfully pointed out that the recitation "for conjugation to a biomolecule for diagnosis and treatment of human animal conditions or diseases" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

It is furthermore respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459

(CCPA 1963). Thus, limitations drawn to the intended use of the instant reagent have not been given patentable weight, i.e., "forming a covalent bond between the reagent and the biomolecule".

Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wilbur et al. in view of Wilbur et al. or in view of Rosebrough as applied to claims 1-9, 11-22, 25, 31-32, 34-39 above, and further in view of Gansoh et al. (5,286,850).

Wilbur et al. is applied as discussed above. The reference lacks preferred DTPA.

Gansoh et al. teach cyclohexyl DTPA as a radioactive ligand for radioimaging.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute cyclohexyl DTPA as taught by Gansoh et al. for DTPA in the invention of Wilbur et al. because of the expectation of achieving similar chelating effects and better chelating effects when an antibody is bound to the chelator. Furthermore, it is within the skill of an artisan in the contrast agent art to substitute one chelating agent for another.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is 571-272-0634. The examiner can normally be reached on M&R (5:30-4).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

lqw

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER